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PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinicopathological conferences held every other Tuesday afternoon at 1:00 P.M., and from the monthly Staff meetings.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $1.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D. C. Please notify on change of address.

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Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

THE ETIOLOGIC RELATIONSHIP OF CHOREA AND RHEUMATIC FEVER

Special Report No. 211

John P. McGovern, M.D.
Joseph M. LoPresti, M.D.

Sydenham's chorea, because of its close statistical correlation with rheumatic fever has long been considered to be a part of the *active* rheumatic process.[1, 2, 3] A review of the early history of this symptom-complex is most revealing with regard to this thought, for in the eighteenth and early nineteenth centuries, chorea generally was considered to be due entirely to psychic factors, especially fear.[4] Stoll[5] in 1780 was probably the first to report cases wherein chorea is a manifestation of rheumatic fever, and he refered to this association as a "loi pathologique." In the mid-nineteenth century, it was not generally known that rheumatic fever is common in childhood and that rheumatic fever is a cause of heart disease, let alone that chorea is often associated with rheumatic fever. As a pioneer and keen observer, Roger[7] undertook to prove all of these relationships at once. In doing so he reported eighty-seven patients in his papers on chorea, all of whom had rheumatic fever. He is justly credited with proving the existence of an association between rheumatic fever and chorea. Unfortunately, however, his convincing presentation led most subsequent observers to overlook the relatively large number of chorea patients who do not have other signs of active rheumatic fever. Cheadle,[8] in the Harvesian Lectures of 1888, wrote in support of Roger's views. Only a few observers, such as Sturges,[9] called attention to a large group in which this association was not clear. Nevertheless, prominent men such as Still[10] regarded chorea to be "just as good evidence of rheumatism as a gumma is of syphilis."

It is the frequent association between chorea and heart disease of the rheumatic type that presents most valid evidence of the interrelationship of the two processes. Table I shows this correlation made by different investigators.[11–27] One must realize that the period of observation in many of these surveys is not clearly delineated, and also that the criteria of what constituted heart disease varied considerably with the investigator. From the various reports in this table, one may note that the average incidence of rheumatic heart disease in chorea patients that were followed is approximately 50 per cent.

In a review by Jones and Bland[24] of 1000 cases of rheumatic fever followed for an average period of eight years, 482 cases demonstrated chorea at some time. The incidence of rheumatic heart disease in this group was 54

per cent. In the remaining 518 patients with rheumatic fever without chorea, 86 per cent developed rheumatic heart disease. The criteria for the diagnosis of rheumatic heart disease were those advocated by the American Heart Association.[28] The lower incidence of heart disease in the group with chorea as contrasted with the non-chorea group is a significant one and suggests the possibility that the chorea in some of the patients might be independent of rheumatic activity and attributable to a totally different etiology. When these investigators selected those patients who exhibited only chorea and no other rheumatic activity during the original

TABLE I

The Incidence of Heart Disease in Chorea Patients

	PER CENT
Osler[11]	51
Marshall[12]	60
Mackie[13]	51.5
Poynton[14]	50
Findley[15]	50
Strong[16]	45
Wallace[17]	41.5
Donkin[18]	42
Abt and Levinson[19]	32
Thayer[20]	27.7
Frazer[21]	63
Koplic[22]	72
Combs[23]	44
Jones and Bland[24]	54
Parish et al.[25]	59.8
Usher[26]	44.7
Schwartz and Leader[27]	73.7

attack, it was found that only 3 per cent developed heart disease during any average eight-year period of observation.

In order further to develop this idea, a term "pure" chorea must be defined. It is taken to classify those patients who exhibit only chorea as evidence of rheumatic fever at the onset and who give no previous history of rheumatic activity. Four surveys[24, 26, 27, 29] have been made that meet these criteria. The findings are summarized in Table II.

A survey by Parrish[25] cannot be included in these groups of "pure" chorea as his use of the term did not fully coincide with the definition given. Table II shows that of the total of 787 chorea patients, 299 (38 per cent) were "pure," and that of these, 77 or an average of 26 per cent developed heart disease during the follow-up periods of observation. Approximately

three-fourths of all "pure" chorea patients did not develop cardiac lesions. This would give support to the concept that chorea and rheumatic fever are not necessarily synonymous.

Having presented the historical background and indicated the importance of the concept of "pure" chorea, our study is an attempt to further classify

TABLE II

The Incidence of "Pure" Chorea and Heart Disease

	NUMBER OF CHOREA PATIENTS	TIME OBSERVED	NUMBER OF "PURE" CHOREA	HEART STIGMATA IN "PURE" CHOREA GROUP
		years		
Jones and Bland[25]	482	8 (average)	134 (28%)	4 (3%)
Usher[27]	105	3	56 (53%)	15 (27%)
Schwartz and Leader[28]	84	1–12	75 (89%)	58 (77%)
Coburn[29]	114	2–10	34 (30%)	0
Total	785		299 (38%)	77 (26%)

TABLE III

Cases of Chorea Studied during a Ten-Year Period (1935–1945)

	CHILDREN'S HOSPITAL SERIES	DUKE HOSPITAL SERIES	TOTAL
Consecutive Number of Admissions	44	47	91
Patients included in Series	36	43	79
Number of patients seen during initial attack	28	37	65
Number of patients seen during subsequent attack	8	6	14
Number of white patients	22	35	57
Number of colored patients	14	8	22
Number of males	20	17	37
Number of females	16	26	42
Average age (in years)	8.7	11.7	10.4

this symptom-complex as a distinct entity. The group studied were 91 consecutive cases of chorea admitted to the Duke University Hospital, Durham, North Carolina and to the Children's Hospital, Washington, D. C. during the ten-year period from 1935 to 1945. Of this group, 12 cases were discarded because the data was insufficient for analysis. Of the remaining 79 patients, 36 were from The Children's Hospital and 43 were from the Duke Hospital. Of this group, 65 patients were seen during their first attack of chorea, and the remaining 14 were seen during a second or later

episode. Fifty-seven of the patients were white; 22 were colored. There were 37 males and 42 females. The average age was 10.4 years, the youngest patient being 3 years of age. (See Table III.)

In active rheumatic fever, an increased erythrocyte sedimentation rate is considered to be an almost constant finding, except in the presence of cardiac decompensation and in some cases of chorea. The following analysis was planned to consider the differences, if any, between those patients with increased and those with normal erythrocyte sedimentation rates, particularly to note if a significantly larger number of "pure" chorea patients would fall into either grouping. Erythrocyte sedimentation rates were done by the Wintrobe method, considering over 10 millimeters per hour corrected as elevated.[33] Of the 65 patients seen during their first episode of chorea, 43 (66.2 per cent) had erythrocyte sedimentation rates which were above normal and 22 (33.8 per cent) were within normal limits.

TABLE IV

Patients Studied during Initial Episodes of Chorea

	AUTHOR'S SERIES TOTAL SUBJECTS—65	KAGAN AND MIRMAN'S SERIES TOTAL SUBJECTS—88
Group No. 1—Patients Treated with Increased E. S. R.		
Number with increased E. S. R.	43 (66.2%)	37 (42.0%)
"Pure" Chorea	21 (48.8%)	6 (16%)
"Non-Pure" Chorea	22 (51.2%)	31 (84%)
Average E. S. R.	25.6 mm/hr.	
Group No. 2—Patients with a Normal E. S. R.		
Number with normal E. S. R.	22 (33.8%)	51 (58.0%)
"Pure" Chorea	12 (54.5%)	50 (98.0%)
"Non-Pure" Chorea	10 (45.5%)	1

In Group 1 (Table IV) are the patients with elevated erythrocyte sedimentation rates (average 25.6 millimeters per hour corrected with only 2 below 14 millimeters per hour corrected). Twenty-one (48.8 per cent) of these had "pure" chorea by our definition. Of the remaining 22 (51.3 per cent) cases, 3 gave only a past history suggestive of rheumatic fever with the chorea; 7 had accompanying rheumatic manifestations with the chorea but gave no history of previous rheumatic activity, and 12 had both history and other evidences of active rheumatic fever concurrent with the chorea.

Of the 22 (33.8 per cent) patients in Group 2 (Table IV) with normal erythrocyte sedimentation rates (average 5.8 millimeters per hour cor-

rected), 12 (54.5 per cent) were "pure" chorea and 10 (45.5 per cent) can be considered "non-pure" chorea. Of these 10 patients, 2 gave only a history of rheumatic fever with the chorea; 6 had accompanying rheumatic manifestations with the chorea but gave no history of previous rheumatic activity, and 2 had both history and other evidences of active rheumatic fever concurrent with the chorea.

A similar analysis of 88 patients from the Chicago area seen during their first episode of chorea was made by Kagan and Mirman.[32] In their group division, 51 (58 per cent) of the patients had normal erythrocyte sedimentation rates corresponding to our 22 (33.8 per cent) in Group 2 (Table IV). They state that none of these patients showed any other evidence of active rheumatic fever during their admissions and only one gave a history of rheumatic activity. Furthermore, 29 of these cases failed to develop rheumatic fever subsequently during a follow-up period of from one to eleven years. In spite of a normal sedimentation rate only 12 (54.5 per cent) of our 22 patients met the requirements for "pure" choreas as contrasted to 50 (98 per cent) in Kagan and Mirman's series. The per cent difference (33.5 per cent) is statistically significant.

In a comparison of the patients in Group 1 with erythrocyte sedimentation rates above normal, again a divergence is noted in our group when compared with that of Kagan and Mirman. Thirty-seven (42 per cent) of their patients had erythrocyte sedimentation rates above normal, of which 31 (84 per cent) had other evidence of rheumatic activity at the time of the chorea episode. Of our 65 patients seen during the initial episode of chorea, 43 (66.2 per cent) had elevated erythrocyte sedimentation rates, of which 22 (51.2 per cent) cases did not meet the criteria of "pure" chorea. The per cent difference (32.8 per cent) between the two "non-pure" chorea groups, 31 (84 per cent) versus 22 (51.2 per cent) is statistically significant as is the per cent difference between the "pure" chorea groups, 21 (48.8 per cent) and 6 (16 per cent). From these observations we are unable to substantiate the conclusions of Kagan and Mirman that patients who have a normal erythrocyte sedimentation rate during their first episode of chorea fit into the classification of "pure" chorea; nor can we find from our series that chorea associated with an increased erythrocyte sedimentation rate is in most instances a manifestation of active rheumatic fever with evidence other than just the chorea. A comparison of their total patients studied during the first attack of chorea (88) with the author's (65) reveals that the per cent differences between the number of patients with elevated erythrocyte sedimentation rates, 42 per cent versus 66.2 per cent, is statistically significant. This difference applies to those with normal erythrocyte sedimentation rates also. This would indicate that the selections of patients were from different statistical universes and that chorea in more southern areas may manifest itself differently from that in a northern area.

Of our total of 79 patients with chorea, 14 (15.2 per cent) were not seen during the first episode of chorea but were seen for the first time during the second or subsequent choreic episodes (Table V). Five of these had a normal erythrocyte sedimentation rate (average 8 millimeters per hour) of which 2 could be called "pure" chorea. Nine of these had normal erythrocyte sedimentation rates, all of which met the criteria of "pure" chorea. Although the number of cases is small, the difference is apparent.

In addition to an elevated erythrocyte sedimentation rate, fever and leukocytosis are associated with rheumatic activity. However, McCul-

TABLE V

Patients Seen for the First Time during Subsequent Attacks of Chorea

	AUTHOR'S SERIES (79 CASES)	KAGAN AND MIRMAN'S SERIES (107 CASES)
Number of patients with subsequent attacks	14 (15.2%)	19 (22.7%)
Number of patients with normal E. S. R.	5 (38.0%)	9 (47.4%)
Number of "Pure" Chorea	3	9 (100%)
Number of patients with increased E. S. R.	9 (72.0%)	10 (52.6%)
Number "Pure" Chorea	3	0

TABLE VI

Leukocytosis in 79 Patients with Chorea

	"PURE" CHOREA	"NON-PURE" CHOREA
Number of patients	39	40
Number with leukocytosis	9	9
Number with normal E. S. R.	2	4
Number with increased E. S. R.	7	5

loch[32] stated that there is no leukocytosis in chorea as well as an absence of fever. Swift[33] noted that:

> In the absence of evidence of concomitant non-rheumatic infection, a persisting leukocytosis signified persistence of rheumatic infection, and conversely that repeated normal counts indicated that the attack was drawing to a close.

Swift used 8,000 to 9,000 white blood cells per cubic milliliter as the upper limits of normal and thus 10,000 was considered to be a definite leukocytosis. Of our 39 patients who met the criteria of "pure" chorea (Table VI) only 9 demonstrated leukocytosis by Swift's standards. Of these 9 cases, 7 also had increased erythrocyte sedimentation rates. Of our 30 "non-pure" chorea patients, 9 also showed a leukocytosis. Of these, 5 had increased

erythrocyte sedimentation rates. From this data, one might infer that the incidence of leukocytosis is as high in a "pure" chorea group as in a "non-pure" group. Although the number is small, the data indicates that in the presence of an increased erythrocyte sedimentation rate, leukocytosis is more prevalent both in the "pure" and in the "non-pure" groups.

A review of our data with regard to fever shows a close correlation between this measurement and leukocytosis, so close in fact that the correlations made with leukocytosis also apply to fever.

The differential white count in our series reveals the presence of an eosinophilia in 20 (25.3 per cent) of our 79 cases. The criteria for eosinophilia were those of Page[34], in which a 5 per cent eosinophil count is taken as significant. Stool cultures were negative for parasites in all of these cases as was the history for allergic disorders. An attempt was made to correlate the incidence of eosinophils in "pure" and "non-pure" groups, with increased and normal erythrocyte sedimentation-rate groups, with leukocytosis, and with the multiple correlations of these three factors. No correlation was found, there being an approximately equal distribution throughout. One may conclude that the presence of eosinophilia is of no value in the differential analysis of chorea patients although it is a frequent finding.

Freedman and Holtz[35] stated that in acute rheumatic pericarditis and arthritis the eosinophils are absent or diminished in number during the height of the disease but that during the stage of recovery the eosinophils reappear and there is post-infectious eosinophilia as in other acute infections. They believed that recurrent and continuous eosinophilia indicated convalescence. Perry[36] attached little significance to what he termed the usual slight post-infectious eosinophilia with lymphocytosis of acute rheumatic fever and carditis. Swift[37] considered the eosinophilia in rheumatic fever in the light of an allergic manifestation and pointed out the allergic nature of many rheumatic manifestations. He found eosinophilia in only 3 of the 13 cases studied. However, all patients had chorea.[3] Berger's observations[38] are of considerable interest. In a series of chorea patients, comprised of 29 girls and 11 boys examined and found to have no ova in the stools and no history of asthma, he found an average eosinophilia of 7.6 per cent with the highest count 26 per cent and the lowest 0 per cent. He stated that there was no connection between the severity of the symptoms and the percentage of eosinophils found. McCulloch[32] finds that the blood picture is usually normal in chorea, although eosinophilia of 5 to 10 per cent has been found in a surprisingly large number of children.

The electroencephalogram has been used to study the etiology of chorea and its relation to rheumatic fever. Usher and Jasper[39] in a study of 23 children with chorea found that in all the severe cases there were generalized abnormalites in the electroencephalogram. They consider chorea a symptom

of a cerebral disorder as is that of epilepsy. They conclude that there can be little doubt that a severe and generalized abnormality of cerebral function is involved in all severe cases of Sydenham's chorea with or without the usual manifestations of rheumatic fever. This argues against the importance of psychogenic factors, at least in severe cases.

The importance of psychogenic elements and personality factors in the etiology of Sydenham's chorea must be considered. During the years which followed the reports of Roger which led to the thinking of chorea and rheumatic fever as synonymous, others such as Hughes[40] (1855), Gowers[41] (1898), Smith[42] (1886), and Sachs[43] (1905) still considered fright and other psychogenic factors to be most important and they expressed dissatisfaction with the idea that rheumatic fever is the principle or sole cause of chorea. McCulloch[32] points out that the patient's mental and emotional development varies, and that in this respect chorea develops only in those children who have some weak point where the manifestation begins. As to psychogenic factors, he states that, "The familial socio-economic background is generally faulty and furnishes a fertile soil for emotional disturbances to appear." In a study of 150 patients that were followed closely with regard to personality disorders, Gerstley[44] concluded that "our conception of the true nature of chorea has been altered. It now seems to us that chorea is a clinical syndrome rather than a disease entity developing in a child predisposed to it by heredity and constitution, upon exhausting psychic stimulation or various infection factors." He stated that psychic trauma seemed a far more important factor in its etiology that did any type of infection.

Concerning the pathology of chorea, and its likeness or dissimilarity to rheumatic fever, little is known. Rarely has one had the opportunity to examine the brain after death from chorea, as the patients usually recover. The few specimens which have been described showed increased vascularity, a few plasma cells scattered irregularly, and slight edema of the glial structures.[33] These changes may be located throughout the brain but are found chiefly about the basal nuclei. These alterations resemble more closely the exudative type phenomena of rheumatic fever than the proliferative if there be a connection.

Neurologic examination, including spinal fluid examination has uniformly failed to give us any insight into the etiology of chorea.

DISCUSSION

The authors believe that the series evaluated is a representative one. It was selected from two distinctly different medical centers: one a large pediatric hospital drawing its patients from a decidedly heterogeneous

population, the other from a university teaching hospital some 270 miles to the south. The studies performed upon these patients were done independently by competent observers over the same ten-year period, and the methods employed were the same in both institutions. When the patients were divided for analysis on the basis of "pure" and "non-pure" chorea and multiple correlations were applied with increased and normal erythrocyte sedimentation rates, the presence or absence of leukocytosis, fever, and eosinophilia, no statistically significant variance between the two groups could be found. No patient was included in the "pure" chorea group who had any evidence of previous activity by history, or concomitant rheumatic activity with the chorea. A history of frequent sore throats was sufficient evidence to exclude a subject from this group.

Yet, when this series is compared with another apparently representative group from the Chicago area on the basis of "pure" and "non-pure" chorea groupings, with normal and increased erythrocyte sedimentation rates, there is an easily apparent difference which is confirmed by statistical analysis.

A review of the literature revealed significant differences in the incidence of so-called "pure" chorea, and heart disease in chorea, in other series.

We have long been aware of the fact that the severe acute manifestations of rheumatic fever are less frequently observed in children living in the southern latitudes. On the other hand, the incidence of rheumatic heart disease in adults who have lived all of their lives in the south apparently is almost as high as in the north, suggesting that rheumatic fever in southern latitudes tends to run a more insidious course.

One might logically infer that the manifestation of chorea in the southern United States differs from that in the more northern areas. It should be kept in mind that the number of ways in which tissues may react to specific trauma is limited but that under varying conditioning stimuli, one of which can be climate, these reactions may be modified considerably.

SUMMARY

1. A series of 79 chorea patients admitted over a ten-year period to the Children's Hospital and to the Duke University Hospital has been analyzed.

2. In this analysis, no correlations could be made that would characterize the group of "pure" chorea as contrasted to the "non-pure" chorea group.

3. There was no evidence in this series that would indicate that the etiology of chorea is other than rheumatic fever.

4. A review of the literature with regard to the etiology of chorea is included.

ACKNOWLEDGMENT

The authors wish to thank the Department of Pediatrics, Duke University School of Medicine for providing material for this study.

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ACUTE FULMINATING OSTEOMYELITIS

Report of a Case*

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The following report is presented to stress to the medical practitioner that clinical evidence of osteomyelitis warrants early and intensive therapy with the antibiotics if the most favorable outcome is to be obtained.

B. V., an 8 year old white female was admitted to the Children's Hospital on May 3, 1951. The chief complaints were vomiting, delirium, and fever of one day's duration. The patient had been in apparent good health until the day prior to hospitalization when she ingested some green apples. Regurgitation occurred approximately 6 hours later. In the ensuing period she vomited from 20 to 25 times. On the following day, the child became delirious and fever appeared. Shortly before admission, blueness of the hands and feet were noted and an elevated, maculo-papular, erythematous rash appeared on the trunk and extremities. In addition, she was noted to be limping on her right leg.

The family history revealed the presence of asthma in a maternal aunt, and a paternal aunt has diabetes mellitus. The birth, feeding, and developmental histories were non-contributory. The patient has been sensitive to tomatoes. At the age of 6 years, she had an episode of diarrhea, fever, cyanosis, and delirium. She was treated at home with parenteral penicillin and made an uneventful recovery.

The physical examination on admission revealed the temperature to be 103 degrees. The pulse rate was 160 per minute and was thready in character. The respirations were 38 per minute and the blood pressure was 100/70. The patient was a well-developed and nourished white female who was in peripheral circulatory collapse. A generalized cyanosis was present most marked in the hands and feet. An urticarial rash was noted over the entire body. The patient was semistuporous and delirious but responded to external stimulation. The ear drums, pharynx, and tonsils were markedly inflamed. No nuchal rigidity was noted. Generalized abdominal pain was elicited, but no masses could be palpated. When the right knee was passively moved, marked pain was produced, but no other local signs were noted. The neurological examination was normal.

The laboratory findings on admission revealed a carbon dioxide combining power of 44 volumes per cent, a capillary blood sugar of 75 milligrams per cent, a leukocytosis of 45,900 per cubic milliliter with 81 per cent polys and a shift to the left in the Shilling index. The urinalysis was normal.

Immediately after admission, the patient was placed in an oxygen tent and in Trendelenberg position. She was typed and crossmatched and 200 cubic milliliters of blood was administered. Ten cubic milliliters of adrenal cortical extract and 20 milligrams of benadryl were administered intravenously. A spinal puncture was performed and normal fluid obtained. Chloramphenicol was given intramuscularly in a dose of one gram every 12 hours. Continuous intravenous fluids were continued for the next 24 hour period and consisted of isotonic Ringer's solution and 5 per cent dextrose in distilled water.

The morning after admission the patient's general condition had improved dramatically. The blood pressure had risen to 130/80, the cyanosis had disappeared,

* This patient was admitted to the ward service of Preston A. McLendon, M.D.

the patient was oriented, and the urticaria was no longer evident. At this time, however, local findings were noted in the right knee. There was marked tenderness, limitation of motion, heat, redness, swelling, and fluctuation. In view of these findings, sulfadiazine 3 grams daily and penicillin one million units every three hours were instituted. The temperature was septic and ranged from 101 to 105 degrees. An x-ray of the right lower extremity revealed a small area of necrosis in the medial distal portion of the femur, a slight destructive area in the medial condyle of the tibia, and a periostitis in the lateral border of the tibia in its upper third. A blood culture on admission and repeated the next day yielded a profuse growth of *Micrococcus pyogenes* variety *aureus*. This organism was sensitive to 0.5 unit of penicillin and less than 5 micrograms of aureomycin. The chloramphenicol and sulfadiazine were discontinued and aureomycin in a dosage of 250 milligrams every 4 hours was instituted. On the seventh hospital day the patient became afebrile, the white blood count had returned to normal and blood cultures were negative. There was a gradual subsidence of the local findings in the right knee. The x-ray evidence of osteomyelitis remained unchanged. On the sixteenth hospital day all therapy was discontinued and physiotherapy was instituted. The patient was discharged from the hospital on the twenty-fifth hospital day to be followed in the Orthopedic Out-Patient-Department. At the time of discharge there was complete range of motion in the right knee and except for a slight enlargement, all evidences of infection had disappeared.

DISCUSSION

The case which has been presented brings up a number of interesting and speculative points for discussion. On admission, the patient's condition was critical and she was in marked peripheral circulatory collapse. Her status was not dissimilar to that of an acute adrenal insufficiency. Hans Selye has pointed out that under condition of stress, e.g., infection, trauma, burns, and surgical operations, the normal individual will respond in a definite orderly fashion.[1] He has divided this response into two phases, the alarm reaction and the adaptation syndrome. If the stress or injury is of adequate intensity, the sympathetic nervous system will be stimulated. Among other things, the adrenal medulla will be activated to secrete its hormones, viz., epinephrine and nor-epinephrine. These hormones make an individual more alert, mobilize liver glycogen to provide glucose as a source of ready energy for muscle and brain, increase the blood pressure by increasing the cardiac output, but also cause some peripheral vasodilatation, and increase muscular strength. In the adaptation syndrome, the epinephrine (by way of the hypothalmus) stimulates the anterior pituitary gland to secrete its adrenal cortical trophic hormone (ACTH). In turn, the adrenal cortical trophic hormone will cause the adrenal cortex to secrete its corticoids. These adrenal cortical substances increase the utilization of fat as a source of energy, either directly or by conversion to liver glycogen. Furthermore, through the action of the adrenal corticoids on the sweat glands and renal tubules, sodium and water are retained to replenish body fluids. The adrenal cortical hormones thus counterbalance the effects of the

early mobilization and utilization of immediately available energy reserves in the first phase of the alarm reaction. The simplest and most practical measure of adrenal cortical activity is supplied by the circulating eosinophils.[2] If allergy can be excluded, a fall in circulating eosinophils following stress indicates an intact adrenal cortex. In the normal alarm reaction following surgery, eosinophil levels decline to zero within 6 hours after the incision has been made.[3] Roche, Mills, and Thorne demonstrated that the finding of a normal eosinophil count together with signs of shock at that time strongly suggest adrenal cortical insufficiency.[3] This peripheral collapse can be overcome by the administration of ACTH or cortisone. In acute infectious diseases autopsy evidence suggests that some degree of adrenal depletion may be present in fatal cases.[4, 5] While circulating eosinophil counts were not performed on our patient it would seem logical to assume that the initial clinical syndrome of profound shock was caused by a failure of the adrenal mechanism. The dramatic response to the administration of adrenal cortical extract would lend added weight in support of this supposition.

Another interesting point for consideration is presented by our patient. In the past few years, the treatment for osteomyelitis has undergone a marked change. In the past, therapy was entirely surgical and the results, while favorable, occasionally were productive of marked deformities. Treatment and hospitalization of these patients was often prolonged. With addition to our medical armamentarium of the newer antibiotics, particularly penicillin, more stress has been placed on the early medical management of patients with osteomyelitis. The role of surgery in the treatment of these patients is unquestioned. However, medical treatment is a worthwhile and necessary adjunct. Blanke reported 5 cases of acute hematogenous osteomyelitis treated with penicillin.[6] All of these patients had incision and drainage of the affected part and the results were excellent. It must be pointed out that x-ray avidence of osteomyelitis does not occur until 2 or 3 weeks after the onset of clinical symptoms. *A plea is made that if the clinical symptoms warrant a diagnosis of osteomyelitis, then early, intensive, and adequate treatment be instituted even in the absence of roentgen confirmation of the diagnosis.* The shortened hospital stay and the excellent results obtained by early medical management justify such a measure. Our patient was unusual in that x-ray confirmation of the diagnosis was present on the third day of her illness, and surgical interference was avoided.

Finally, our patient exemplifies a dilemma which confronts the practitioner of modern medicine. The large number of antibiotics which are available for the treatment of disease processes implies the question of selection. While it is not feasible to do sensitivity studies on the causative agent in all patients, it is almost mandatory that in certain selected cases such

studies be performed. In the serious illnesses when the causative organism has been isolated, sensitivity studies are an invaluable aid in the selection of those drugs which will prove most effective in eradicating the infection. The sensitivity of organisms to the various therapeutic drugs is no longer an academic question. Crude estimates are readily obtainable within 24 hours and can be performed in any laboratory. The correlation of sensitivity studies and choice of therapy is another stride forward in medicine. In addition, the causative bacteria may prove to be sensitive to more than one drug and two or three drugs can then be used in the treatment of the infection. Experimental evidence indicates that the utilization of drugs in combination produces a synergistic effect, i.e., one drug enhances the action of the other. There is, thus provided, another useful tool in the management of diseased patients.

SUMMARY

1. An interesting patient with fulminating osteomyelitis of hemagtoenous origin caused by *Micrococcus pyogenes* variety *aureus* has been presented.

2. The role of the adrenal gland, the medical management of osteomyelitis, and the choice of therapy have been discussed.

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PARTIAL SITUS INVERSUS WITH LEVOCARDIA

Case Report No. 212

Sanford L. Leikin, M.D.

Situs inversus with levocardia is a complicated and serious anomaly and consists of a lateral transposition of the viscera of the thorax and abdomen with the exception of the major portion of the heart which is in the left chest. The first case was reported by Breschet in 1826. There have been a total of thirty-six cases reported since that time.[2, 3, 4, 5, 6] Abbot has none in her series. Taussig[7] states that it is usually associated with an extremely complicated cardiac malformation. Anatomical variations in the pulmonary valve and artery, systemic venous return, and defects in the auricular and ventricular septa are common. The incidence of this condition is probably much higher but because of the normal position of the heart, barium swallow to determine the position of the stomach is not done.

Forgacs[8] suggests that in this condition, the auricles are transposed since blood from the normally placed liver drains through the ductus venosus to the left horn of the sinus venosus instead of the right horn, resulting in a left-sided right auricle. He cites eight cases to prove this.

Cyanosis, dyspnea, failure to grow and develop well, and a loud murmur are common clinical findings. A palpable or percussible liver on the left, with resonance on the right are expected signs.

The X-ray findings are those of a heart in the normal position with a right or left aortic arch and the gas bubble in the stomach beneath the right leaf of the diaphragm. The transposition of the abdominal viscera is usually complete.

The electrocardiographic findings are variable. Several have had electrocardiograms which show inversion of P_1. Inversion of the P wave in Lead 1 is rather certain evidence that the auricles are transposed. When all complexes in Lead 1 are inverted, the basic malformation is probably a dextrocardia with rotation of the heart back to the left. This is probably the situation in Shaw's[9] case and Thomson's case No. 1.

Case Report A. L. 50-9043

This four month old colored male infant was admitted to the hospital on December 6, 1950 with a history of two previous admissions.

The patient was admitted here initially at five days of age on July 31, 1950 because of cyanosis of his lips and peri-oral region while crying. The pregnancy and labor were uneventful, and he nursed well prior to admission. Physical examination on admission revealed a well-developed, well-nourished colored newborn infant who did not appear ill, but showed peri-oral cyanosis with crying. His pulse was 146 and respirations were 36. The blood pressure was 72/48. The heart at that time showed a regular sinus rhythm, a pulse rate of 146 per minute, and no murmur was

present. The lungs were clear to percussion and auscultation. The liver was palpable 1 centimeter below the right costal margin. Femoral pulsations were present bilaterally.

A hemogram done at that time showed a red blood count of 4,900,000 per cubic millimeter with 20 grams of hemoglobin. The urinalysis was negative. An x-ray of the chest revealed a heart of normal size on the left with a gas bubble in the stomach

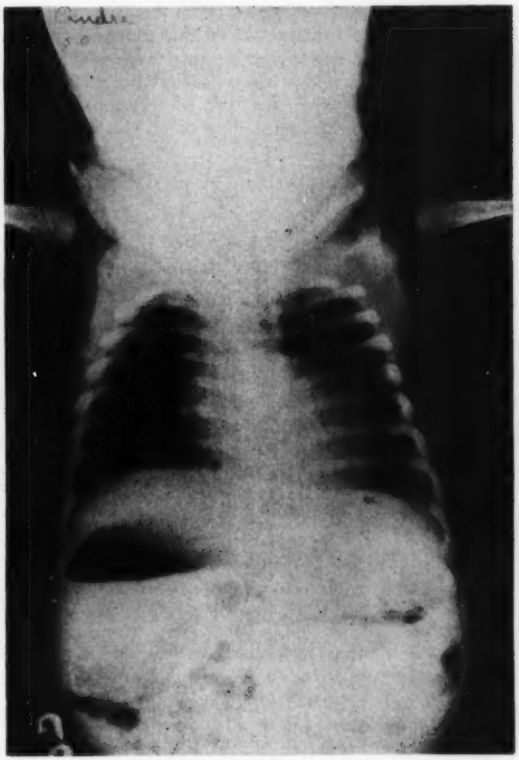

FIG. 1. X-ray showing normal-sized, left-sided heart with dextroposition of the stomach

on the right side; and, barium swallows verified a dextro-position of the stomach without a dextrocardia or displacement of the esophagus. An electrocardiogram showed a sinus rhythm with a rate of 150 per minute. The P-R interval was 0.12 second. The Q-R-S interval was 0.06 second. There was right axis deviation with upright T_1 and T_2 and inverted T_3 waves. The interpretation was right axis deviation.

The patient improved until no cyanosis was perceptible, and he was discharged on August 9, 1950 to be followed in cardiac clinic.

The patient did fairly well after being discharged from the hospital. He was seen in the out-patient clinic on several occasions because of upper respiratory infection with vomiting and diarrhea. These were treated and the patient improved immediately. He was also seen in cardiac clinic on several occasions where moderate enlargement of the right ventricle and a poorly visualized pulmonary artery were noted on fluoroscopy.

He was readmitted to the hospital on October 13, 1950 because of poor appetite of two days' duration and nasal discharge. The mother also described the cyanosis as being more marked. Physical examination on this admission revealed a markedly cyanotic, colored male who did not appear in acute distress. The cyanosis was constant even at rest. The lung bases were clear except for a few ronchi transmitted from the throat. Radial pulses were equal and full. Femoral pulses were present. The heart was not enlarged. The cardiac rate was 120 and the rhythm was regular.

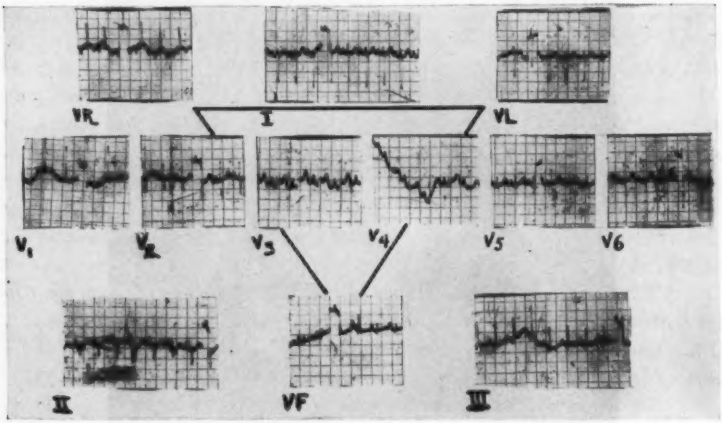

FIG. 2. Electrocardiogram taken on the second admission

The first heart sound was of normal intensity and the second sound was markedly accentuated and extraordinarily pure. There were no murmurs either when the baby was crying or at rest, and the liver was not enlarged.

The red blood cell count was 5,400,000 with 16 grams of hemoglobin. Serology and sickling preparations were negative.

X-ray showed almost complete absence of the pulmonary conus; the aorta made a sharp angle with the ventricle, and the arch appeared to be on the right, although a barium swallow was not obtained. The lung fields were remarkably clear. An electrocardiogram showed the ventricular rate to be 160 with a sinus rhythm, the P-R and Q-R-S intervals being 0.12 and 0.06 respectively. The P_1 was upright. The T waves were upright in leads 1 and 2 and flat in 3. The interpretation was sinus tachycardia and right ventricular hypertrophy.

Immediate treatment consisted of procaine-penicillin, 150,000 units per day and continuous oxygen. Within two days the child became less cyanotic; his chest cleared, and he did well without oxygen. The child was discharged on October 2, 1950 and was to return to cardiac clinic in three weeks.

The final admission, which occurred on December 6, 1950, was preceded by two days of diarrhea. Apparently after the last admission, the child had done fairly well until the day prior to his final entrance to the hospital when he had 12 to 15 loose bowel movements. However, he did not appear ill. On the morning of admission the child appeared weak and was gasping for breath—showing more cyanosis than usual.

Physical examination on this final admission showed the patient to be very cyanotic and in moderate respiratory distress with infrasternal retraction. Both ear drums were injected. There were coarse rales throughout his chest with some

FIG. 3. Interior of heart viewed from the right side showing auricular septal defect, septum primum, common atrio-ventricular canal, and rudimentary ventricular septum.

fine scattered rales which were more prominent in the left chest. The heart was not enlarged to percussion. The rate was 200 by auscultation; the rhythm was regular, and no murmurs were heard. A mass which was felt to be liver was palpable on the right side 3 centimeters from the costal margin. Another examiner thought that the liver was palpable and percussible on the left side.

The patient's hemoglobin was 15 grams per 100 milliliters. The red blood count was 5,600,000 red cells per cubic millimeter. The white blood count was 14,000 per cubic millimeter with 48 per cent neutrophiles, 1 per cent eosinophiles, and 51 per cent lymphocytes. There were 34 nucleated red blood cells per 100 white blood cells. The hematocrit was 76 and the CO_2 content of the blood was 41 volumes per cent.

The patient was immediately placed in an oxygen tent. He was digitalized with a total of 0.1 milligram of digitoxin intramuscularly in divided doses over a period of twenty-seven hours, and improved following this treatment with a reduction in heart rate to 120 per minute. This cyanosis became less marked and the diarrhea cleared, the stools becoming semi-soft on December 7. He still appeared in very acute distress with short and labored respirations on December 8, 1950 and was start d on chloromycetin 50 milligrams every six hours, and also received five drops of tincture of digitalis. At 5:30 P.M. of the same day the infant's pulse and respirations became irregular. Artificial respiration and intercardiac adrenalin were given, but the patient expired.

Gross Examination

The body was that of a poorly developed, fairly well nourished colored male weighing 3.8 kilograms, and measuring 60 centimeters in length. The lips and nail beds had a slight cyanotic tinge, but clubbing was not noted.

On opening the thorax and abdomen, the major portion of the heart was found in the left pleural cavity; the liver edge was 0.5 centimeter above the costal margin in the right midclavicular line and 0.5 centimeter below the left costal margin in the left midclavicular line. The stomach was found to the right of the midline and the ileocecal junction was found in the right lower quadrant of the abdomen.

Both lungs had three lobes and section showed marked pulmonary congestion. The right and left lobes of the liver were of approximately equal size, but the inferior vena cava, which usually has its position to the right of the quadrate lobe, lay to the left. The gall bladder lay beneath the right lobe of the liver in normal position. With the stomach in the right upper quadrant the duodenum passed posteriorly, upward, and to the left. The second part lay to the left of the midline and descended along the margin of the head of the pancreas. It was into this portion that the pancreatic and common ducts emptied. The third portion passed to the right followed by the fourth portion. The majority of the pancreas lay to the right of the midline with the tail extending to the right and the head lodged in the curve of the duodenum.

Description of the Heart

The major portion of the heart lay in the left chest. The right auricle was somewhat dilated and hypertrophied. There was a right-sided superior vena cava which drained into the right auricle and two hepatic veins arose from the posterior surface of the liver and entered the right auricle in the position usually occupied by the inferior vena cava. All four of the pulmonary veins drained into the right auricle. A persistent left superior vena cava and a left-sided inferior vena cava, which received the left hepatic veins, entered a small left auricle. The coronary sinus was not present, but numerous openings of small coronary veins were seen in both auricles.

There was a defect in the auricular septum measuring 0.5 centimeter in diameter and a large defect existed between all four chambers which measured 2 centimeters in diameter. The common orifice between the auricles and ventricles was guarded by a single large valve of the tricuspid type.

A rudimentary ventricular septum was present and was placed somewhat to the left of the position usually occupied by this structure.

Both ventricular walls were hypertrophic measuring 1 centimeter in thickness. There was complete pulmonary-valve atresia, and the pulmonary artery was a fi-

brous cord, measuring 0.2 millimeter in diameter, originating posterior to its normal position and to the left of the aorta. The lumina of the major branches of the pulmonary artery were patent at its bifurcation, and measured 3 millimeters in diameter. The ductus arteriosus was patent and united with the left pulmonary artery.

The aorta arose anterior and to the right of its usual position, receiving blood from both ventricles. Three semi-lunar valves were present. The ostia of the coronary arteries originated in their usual position. The innominate, left carotid, and left subclavian arose in this order from the arch of the aorta which descended on the left.

Microscopic examination of the tissues demonstrated vascular dilatation and enlargement throughout all of the tissues of the body, moderate hypertrophy of the cardiac muscle fibers and calcific material within the arteriolar lumen and wall in one section of the lung.

The pathological diagnoses were:

1. Levocardia with situs inversus.
2. Persistent left superior vena cava.
3. Left inferior vena cava.
4. Anomalous drainage of all pulmonary veins, and right hepatic veins into right auricle.
5. Absence of coronary sinus.
6. Auricular septal defect.
7. Common atrioventricular canal.
8. Pulmonary valve and artery atresia.
9. Partial transposition of the great vessels.
10. Patent ductus arteriosus.
11. Dextroposition of the stomach, duodenum and pancreas.
12. Absence of the spleen.
13. Myocardial hypertrophy.
14. Vascular engorgement of the viscera, chronic.

Bernice G. Wedum, M.D.:

One gains the impression when studying this heart that the magic words of the children's game, "Still pond, no more moving" were pronounced over it in embryonic life when it was about 40 days old and 2.5 millimeters in size. There is no sign of a septum secundum, no evidence of a coronary sinus; both anterior cardinal veins (superior venae cavae) persist; the drainage from the abdominal viscera is partly into the right and partly into the left-sided auricle and the entire pulmonic venous return is the right-sided auricle. Only a rudiment of the ventricular septum is present, and though partitioning of the truncus is complete, the pulmonary artery is atretic. Careful examination of the base of the pulmonary artery reveals that it has two separate origins. The explanation for this is not yet clear.

Whether abnormal venous currents reaching the sinus venosus from the transposed abdominal viscera were the factors initiating the malformation of the heart is a controversial point. It seems more likely that some extrinsic factor was responsible since the auricles and ventricles seem to have ceased developing simultaneously.

This heart resembles the heart of a skate, one of the Elasmobranch fishes, far more than it does the normal human heart. Functionally, there is but a single auricle, a single ventricle, and a single great vessel arising from the base. As long as the fetus led a marine existence, this heart supported growth and development adequately, but was compatible with life for only a brief period following birth.

It is possible to accurately diagnose this malformation during life. The full pulses, the loud, very pure second sound, X-ray findings of a sharp angulation of the shadow of the great vessels with the cardiac shadow in the anterior-posterior position and the remarkably clear lung fields point to the diagnosis of truncus arteriosus with bronchial arteries supplying blood to the lungs or so-called pseudo-truncus arteriosus with atresia of the pulmonary valve and main pulmonary artery and blood supply to the lungs by way of a ductus arteriosus. The complete absence of a murmur suggests a very large defect in the ventricular septum since a murmur is usually heard with a truncus arteriosus.

The presence of anomalies of the venous return could be predicted on the basis of a knowledge of the embryology and a study of cases which have been previously reported.

One decides whether a pulmonary artery is present or not by careful study of the hila of the lung fields by fluoroscopy, after thoroughly accommodating the eyes, and by angiocardiography. If there is any doubt about this point and a competent surgical team is available, a thoracotomy should be done since a right or left pulmonary artery large enough to permit an anastomosis may be found even though there is atresia of the main pulmonary artery. In this case, although small right and left pulmonary arteries were present, little benefit could have been expected from the operation because of the other anomalies present.

The electrocardiogram in this case is of great interest. Right bundle branch which is often found in auricular septal defects is not present; indeed there is no sign of intraventricular block in spite of the fact that the ventricular septum is practically absent. Anatomically, it is not possible to tell which is right and which is left auricle in this heart. The P wave in AVR and in Lead 1 is upright, which suggests that the sino-auricular node is in the right sided auricle at the base of the right-sided superior vena cava. If the sino-auricular node were in the left-sided auricle one would expect to find the P wave in both these leads inverted as in an uncomplicated dextrocardia. We hope to dissect out the sino-auricular node and bundle of Hiss in this specimen.

I should like to express my indebtedness to Dr. W. R. Milnor for helpful comments on these tracings.

SUMMARY

1. The literature on situs inversus with levocardia is reviewed.
2. A case report of this anomaly with autopsy findings is reported.

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THE USE OF CHLOROMYCETIN PALMITATE IN INFANTS AND CHILDREN*†

Special Report No. 213

Sidney Ross,M.D.
Frederic G. Burke, M.D.
E. Clarence Rice, M.D.

In the pediatric field, the administration of powdered crystalline chloromycetin has been attended by considerable difficulty especially in infants and young children in view of the extreme bitterness of the drug. Attempts to disguise the taste in palatable vehicles has generally met with only partial success. When administered by trained nursing personnel, infants in the hospital can be persuaded to take the drug by dint of persistence and not infrequently by force; however, at home, the average mother encounters a real problem in administering powdered chloromycetin, and all too often is rewarded for her efforts by prompt vomiting of the drug

* From the Research Foundation of Children's Hospital, Washington, D. C.

† Chloromycetin palmitate was generously supplied by Dr. E. A. Sharp, Parke-Davis Co., Detroit, Michigan.

shortly after its ingestion. Because of this, the opportunity of employing as useful a drug as chloromycetin in the pediatric age group has been somewhat circumscribed.

Recently an ester of chloromycetin has been prepared in which the terminal hydroxyl group of the propane diol side chain has been replaced with an ester group producing chloromycetin palmitate.[1] This ester contains 57.6 per cent of chloromycetin base and is completely lacking in the bitter taste found in crystalline chloromycetin. However, chloromycetin palmitate per se possesses practically no antibiotic effect (1 per cent of the antibiotic activity of chloromycetin by bacteriological method of assay). The antibiotic action of the ester depends upon the rate of hydrolysis to the free alcohol form of chloramphenicol. Several factors would theoretically

CHART 1

A. CHLOROMYCETIN (CRYSTALLINE)	BLOOD LEVELS (MCGMS PER C.C.)					
	½ hr.	1½ hrs.	3 hrs.	5 hrs.	8 hrs.	12 hrs.
1	22	30	15	11	2.4	0
2	11.3	22.6	15	7.5	3.8	0
B. CHLOROMYCETIN (PALMITATE)						
1	2.2	8.3	4.5	6.4	3.0	0.3
2	3.7	12.3	8.6	11.2	4.8	2.2
3	1.1	9.5	11.8	10.0	5.4	2.8

determine the rate and degree of hydrolysis. Perhaps among these, the most important are the emulsification through the action of the bile and the splitting action of intestinal lipases.

Pharmacological experiments performed on chloromycetin palmitate indicate that the ester is less toxic than crystalline chloromycetin to mice, rats, and dogs in a ratio of 2:1.[1] In dogs, it is absorbed and/or hydrolyzed in the intestinal tract in such a ratio that the initial blood concentration is present at about eight hours after administration. About 1.5 per cent of the ester is excreted in the urine of dogs in an unchanged form. However, urinary excretion of chloromycetin continues for a considerable period of time after the blood levels have fallen to a low level.[1] This suggests that absorption of the chloromycetin and its deposition in the tissues occurs rapidly, followed by a slow continuous release.

In order to compare the rate of absorption of chloromycetin palmitate

with crystalline chloromycetin, a preliminary experiment was done whereby doses of 20 milligrams per kilo of body weight were each given to three children ranging in age from two years to four years. The dose of chloromycetin palmitate was calculated in terms of chloromycetin base (57.6 per cent of chloromycetin palmitate). The results are noted in Chart 1. As will be observed, relatively high blood levels were noted within one-half hour after administration of crystalline chloromycetin with maximum levels being achieved after about one and one-half hours followed by a gradual tapering off in blood concentrations within the next six hours. Sub-optimal titers were observed after eight hours and no chloromycetin content was noted after twelve hours. A somewhat different absorption curve was obtained after ingestion of chloromycetin palmitate. Lower blood levels ranging from 1.1 to 3.7 micrograms per cubic millimeter were observed after one-half hour and relatively constant titers ranging from 4.5 to 12.3 micrograms per cubic millimeter were observed from one and one-half hours to five hours after ingestion of the palmitate. Blood levels in all three patients receiving the chloromycetin palmitate were still demonstrable even after twelve hours following ingestion of the drug. This indicates a less rapid absorption of chloromycetin palmitate, the delay being due to the hydrolyzing of the ester by the lipolytic enzymes in the intestinal tract. Thus the blood levels obtained after administration of chloromycetin palmitate were generally of a lower order of magnitude than that obtained with crystalline chloromycetin when identical doses were employed. Similarly, the titers were more prolonged with chloromycetin palmitate due to the slow continuous release of chloromycetin following hydrolysis.

CLINICAL RESULTS

Forty patients in the pediatric age group have been treated thus far with chloromycetin palmitate at The Children's Hospital and daily blood levels in these cases have been obtained after administration of the drug. The group of cases included eight patients with shigella dysentery; two patients with salmonella enteritis, seventeen patients with non-specific diarrhea and dehydration and thirteen patients with upper respiratory infections including pharyngitis, tonsillitis, and otitis media. With the exception of two instances, the dose of chloromycetin base was 140 milligrams every four hours (250 milligrams of chloromycetin palmitate).

The results obtained in these forty cases were comparable in every respect to those noted with crystalline chloromycetin. For example, in the eight patients with shigella dysentery, the stool cultures were rendered free of the pathogen within twenty-four to forty-eight hours after initiation of chloromycetin palmitate and remained negative during the ensuing six days

of therapy. This represented a result comparable to that obtained in thirty-five cases of shigella dysentery which we have treated with crystalline chloromycetin.[2] A salutary effect of the drug was also observed in the two cases of salmonella enteritis. The course of the disease in the respiratory group was similarly affected favorably by the chloromycetin palmitate. The results in the seventeen patients with non-specific diarrhea were difficult to assess; however, the prime reason for employing the ester in this group was to determine whether hydrolysis of the drug would occur in normal fashion in infants with gastro-enteritis.

Daily blood levels were obtained on each of the forty patients for three to six consecutive days while on chloromycetin palmitate therapy. The blood levels were usually drawn approximately one-half hour to one hour before the succeeding dose of the drug. It was observed that a dose of 25 to 50 milligrams per kilo of body weight per twenty-four hours yielded sub-optimal therapeutic titers while a dose of 50 to 100 milligrams per kilo of body weight per twenty-four hours produced adequate therapeutic titers in a goodly proportion of the patients. When 100 to 150 milligrams per kilo of body weight per twenty-four hours was employed the blood levels achieved were in good therapeutic titer except in very few instances. On the other hand, a dose of 150 to 250 milligrams per kilo of body weight per twenty-four hours produced consistently high titers which were usually in excess of the recommended therapeutic blood level required for most susceptible infections (i.e., 10–20 micrograms per cubic centimeter).

Thus, if one were to employ chloromycetin palmitate in the age group where it would have its greatest usefulness, namely, in the six-month to three-year old child, our recommended dose would be 100 to 150 milligrams per kilo of body weight per twenty-four hours in a four to six hour divided dosage schedule. With this dosage, one can be fairly well assured of a therapeutic blood titer ranging between eight to thirty micrograms per cubic centimeter.

There was no evidence of toxicity with chloromycetin palmitate in any of our patients. All the children, irrespective of age, tolerated the palmitate ester very well and no instance of vomiting, anorexia, or diarrhea was observed. Occasionally, an older child would make mention of a "funny taste" in his mouth an hour or so after administration of the drug but in no sense was it a disturbing complaint nor did it discourage continuing acceptance of the drug.

In all likelihood, chloromycetin palmitate will enjoy a wide range of usefulness in the pediatric age group because of its palatibility and therapeutic efficacy. The apparent readiness with which the drug was hydrolyzed in all our patients, irrespective of age or nature of illness, was encouraging. Of singular interest were the results obtained in a proven case of pancreatic

fibrosis who received chloromycetin palmitate. It was found that the daily blood levels obtained in this child were, to a first approximation, similar to those observed in the other patients in spite of the depression of the pancreatic lipases. In all probability, the lipases contained in the succus entericus were sufficient to hydrolyze the palmitate ester.

REFERENCES

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